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# Determination and Distribution of Arsenic in Certain Body Fluids after the Injection of Arsenobenzol, Salvarsan, and Neosalvarsan.

By C. N. MYERS, Organic Chemist, Hygienic Laboratory, United States Public Health Service.

The retention of heavy metals by different organs and body fluids has received considerable attention from those who are interested in chemotherapy. However, the amount of heavy metal is very small and the distribution is widespread, which facts call for a method capable of detecting a very small amount of any given element. Analytical methods and procedures, therefore, demand a careful study of the conditions necessary to isolate any one of these elements, which in most cases has been administered in therapeutic doses. It is readily realized that after administration and absorption of these elements the amount found in any one organ is relatively small.

From the investigations of Fischer and Hoppe (1909), Gæbel (1911), Gautier (1899, 1917), Greven (1910), Kobert (1906), Lehmann (1912), Lockemann (1911, 1913), Rupp (1911), and many others, it was early realized that the amounts of arsenic sought after would be extremely small and that an exact method was essential for the success of this work.

The first steps undertaken in these determinations were to obtain satisfactory control experiments. The reagents which were to be used in these analyses were carefully selected and then tested for arsenic by the modified Marsh-Berzelius method described in this article. As a result of this investigation it was early learned that the label on the reagent bottle (even though it may indicate that there is no arsenic present) is not sufficient or final evidence that the product is not contaminated by arsenic (Myers, 1916). With these facts in mind it is advisable to test all of the reagents which are to be used at any stage of the determination. After having been convinced that the reagents are free of arsenic, in the sense that in given quantities no detectable amounts are present, then the control experiments may be started. (It is understood that no reagents are absolutely free from impurities, but that if sufficient quantities are used determinable amounts may be found.)

At this point a brief note in regard to so-called "normal" arsenic should be made—a question which has involved considerable discussion. Gautier (1899) summarizes his results in the following words: "I would state that arsenic, aside from the thyroid, mammary, and thymus glands, never occurs in the human body except in the skin, hair, bones, milk, and sometimes in the fæces, and then only in traces." Warren (1915) points out that there is no such thing as normal arsenic, and if found in the body it has come from some external source (medicinally or criminally). Kunkle (1915) says if there be a so-called normal arsenic it is exceedingly small (0.01–0.001 milligram in an organ). More recently Klason (1916) draws the conclusions from his analyses of urine that "arsenic is a normal constituent of the human body, and consequently its use as a medicine (compare iron) can be understood." Further discussion of this subject will be found in another paper discussing the amounts of arsenic found in various parts of the body. These quotations clearly indicate a difference of opinion on this subject.

In order to test the control method it is necessary to make experiments which are very similar to those by which we examine the blood and other fluids in question. Twenty cubic centimeters portions of normal guinea-pig blood are obtained and placed in porcelain casseroles. Six of these samples are used in the following manner: Sample No. 1 is used exactly as it has been obtained from the animal, while the remaining four samples are added to solutions containing 1, 3, 5, 7, and 10 parts, respectively, per million of arsenic. In this manner we have a blank experiment and five solutions containing different amounts of arsenic. At least four sets of these experiments were carried out in order to test the method which was to be used. Enough of the reagents was blanked in this way so that the entire set of experiments was uniform.

Most heavy metals enter into chemical combination with body proteins, and it has been found necessary to decompose the organic matter present in order to make an analysis of the metal. The samples which are contained in the porcelain casseroles are now treated drop by drop with a mixture of fuming nitric acid and concentrated sulphuric acid in the proportion of 100 cubic centimeters of the sulphuric acid and 900 cubic centimeters of fuming nitric acid (each arsenic free), the reaction being allowed to take place in the cold after the addition of a few drops of this mixture. A rapid addition of acid will cause foaming, spattering, and charring. It is well to allow this mixture to stand half an hour if there are indications of a violent reaction. Color changes may take place in serum, clot, and spinal fluid. The entire mass is now placed on the water bath and allowed to digest. If there is no vigorous action, 7 cubic centimeters of acid may be slowly added. Upon further digestion a thick, oily liquid is obtained. If the above reaction is not carefully guided, there will be a loss of arsenic from excessive foaming, from spattering, or from a sudden charring of the whole mass, which may cause a loss of arsenic in the smoke evolved. It is found that

10 to 12 cubic centimeters of this acid mixture will *apparently* destroy the organic matter in 20 cubic centimeters of blood. To this yellow oily material 15 grams of equal parts of a mixture of solid potassium and sodium nitrates are added in saturated aqueous solution. The alkali metals here unite with the arsenic while further oxidation of the blood takes place. This mixture is evaporated on the water bath and a yellow crystalline mass remains, which still contains traces of organic material. Equal parts of sodium and potassium nitrates are mixed and ground in a mortar. Ten grams of this mixture are fused in a platinum dish, and the yellow crystalline mass is slowly added to the fused salts.

Considerable care should be exercised at this stage of the analysis. Too rapid addition may cause charring, and hence a loss of arsenic, or, in the case of material containing much oil or fat, there will be a brownish froth formed which will creep over the sides of the dish. As low a temperature as possible is used at first; finally a free flame is applied, and the entire mass is fused. The fused mass is allowed to cool and it is then dissolved in water; after the addition of sulphuric acid, it is heated upon a water bath, when there is an evolution of nitrous fumes. By repeating this last step, practically all of the nitrates are removed.

The next step in the method consists in the adsorption of the arsenic by means of ferric hydroxide. The solution as obtained above is neutralized quite exactly with ammonia, as, in the course of these analyses, it was observed that an excess of ammonia interfered with adsorption. According to the theory of adsorption, an optimum hydrogen ion concentration is required for adsorption; i. e., there is an optimum condition of surface affinity in the exchange of electrical charges. Exact electrometrical measurements should be made, so as to define the limits of hydrogen ion concentration within which adsorption of the metal by another takes place in the conditions under observation. In carrying out this process three adsorptions were performed, by adding successive portions of 15, 10, and 5 cubic centimeters of ferric ammonium sulphate to the solution containing arsenic. The solution of iron alum is so prepared that 1 cubic centimeter contains 50 milligrams of ferric hydroxide. The exact amount of ammonia necessary to precipitate the ferric hydroxide is added to the solution while cold, for the reason that adsorption is aided by low temperatures. Two hundred and twenty-six grams of ferric ammonium sulphate, dissolved in water and made up to 1 liter, yield a solution satisfactory for this purpose. The second adsorption is carried out with the filtrate from the first procedure by using 10 cubic centimeters of iron solution. This is neutralized and treated as indicated above. The filtrate in this step is treated with 5 cubic centimeters of iron solution and precipitated. It is now necessary to wash the combined precipitates of ferric hydroxide with distilled water to remove the ammonia salts and traces of nitrates. This may be done in an ordinary funnel with filter paper or with carefully prepared asbestos. The filtrate consisting of the wash water should give no test for nitrates. The precipitate is just dissolved in dilute sulphuric acid (10 per cent) and made up to a definite volume; in this investigation 100 cubic centimeters were found to be convenient. All of the solutions used in this investigation were obtained by a uniform procedure, and all steps in the analyses were carried out as uniformly as possible. In this manner the samples to be examined were prepared for the Marsh-Berzelius test. All of the control experiments were treated as described above.

*Marsh-Berzelius test.*—In carrying out this part of the analysis an accuracy of 1 part per million was sought after. With this in mind, carefully selected reagents were used, and in every step known amounts of reagent were added. On this basis a set of standard mirrors was prepared, ranging from 1 to 10 parts per million. Three sets of mirrors were prepared in order to observe whether the standards could be reproduced, and an affirmative finding was obtained. However, at this point a little care in the manipulation is required to control the rate of evolution of the arsenuretted hydrogen, the decomposition of the gas, and the deposition of the metallic arsenic in a uniform and evenly spaced portion of the capillary, which is properly cooled.

A tenth normal solution of arsenious oxide is used as a starting point. The solution is accurately standardized just before using, and from this the other dilutions are obtained. The final dilution is so prepared that 1 cubic centimeter of arsenious acid solution contains 1 part per million of metallic arsenic. The solution is used soon after preparation, for the reason that there is some evidence that these dilute solutions are very unstable. Mirrors are prepared by using from 1 to 10 cubic centimeters of this solution and carrying out the Marsh-Berzelius procedure. These mirrors were compared with those which are obtained by using organic material (guinea pig blood) and the agreement was found to be good. These results indicated that the method of destroying the organic material was reasonably good, and that the loss, if any, was very small. The mirrors were sealed off in an atmosphere of hydrogen and kept in the dark. From time to time mirrors from the unknown materials were compared with the standards. In the lower range of the scale it seemed possible to detect differences of less than 1 part per million, but since the personal equation may vary from day to day no attempt was made to pursue the matter further. The method is obviously a relative one and the readings were averaged; thus, a

1.3 mirror is recorded as 1, while 1.7 would be recorded as 2. It was realized that this might lead to some discrepancies with unknown solutions, for the reason that aliquot portions were necessary both as a means of obtaining duplicate mirrors and as a method of getting a preliminary idea as to the amount of solution which should be used to keep within the range of 1 to 10 parts per million. Mirrors containing larger amounts of arsenic do not show small differences as readily as does the range of 1 to 10.

*Procedure.*—As it has been found very difficult to secure arsenic-free zinc, it is very essential to examine this reagent with extreme care. Fifty grams of zinc were placed in the bottle and 100 cubic centimeters of concentrated sulphuric acid, diluted to a 25 per cent solution, are allowed to act on the zinc with the evolution of hydrogen. The acid is allowed to drop into the bottle from a small dropping funnel, and the evolution of gas is continued over a period of five hours. If any arsenic is present it will be hydrogenated and decomposed, as illustrated in the following plate. If at the end of this period no appreciable mirror is formed, it is safe to say that the zinc and sulphuric acid will cause no difficulty by yielding a mirror in this interval.

The sample to be examined is carefully weighed and transferred to a porcelain casserole of suitable capacity. The fluid is then treated with 7 cubic centimeters of nitrosulphuric acid mixture allowing the acid to drop in very gradually. In case of foaming or tendency toward charring the addition of acid is stopped until the violent reaction has subsided. The mixture is digested on the water bath until the material has a yellow oily appearance. Seven cubic centimeters of acids is usually sufficient to destroy at least 10 grams of fluid. The addition of a saturated solution of potassium and sodium nitrate is now carried out. The scheme employed in the control method is now carried out. In making the Marsh determination it was found suitable to make up all the solutions to 100 cubic centimeters and then use an aliquot (usually 10 cubic centimeters) to get an idea of the amount of arsenic present. This preliminary step was followed by duplicate determinations which were compared with the 10 standards. The results were expressed either in parts per million or in milligrams per 100 grams of material. The samples used in these investigations usually weighed between 5 and 20 grams. These amounts were sufficiently large for duplicate determinations, but the application of this method should be determined by the conditions.

*Apparatus.*—A brief description of the apparatus follows: A bottle of convenient size for the work in question is selected. It is well to select a good hard glass bottle of about 300 cubic centimeters capacity and then treat it several times with warm sulphuric acid ("C. P.") and zinc ("C. P."). A two-hole rubber stopper is boiled out in dilute acid and dilute alkali. Into this stopper place a dropping funnel which has been drawn to a small opening. This should extend below the opening of the exit tube, which is provided with two openings at the inner end to prevent the mechanical passage of moisture into the drying material. The drying tube is provided with lead acetate paper and allowed to extend as far as the first bulb. This will dispose of any hydrogen sulphide or selenium compound that may be formed, and also be sufficient in quantity to run several determinations. Anhydrous calcium chloride is then distributed in the remaining bulbs, and at the end of the tube a small plug of cotton is placed to prevent striking back of the ignited gases. The best Jena glass tubing is used for the deposition of the mirrors. Some Jena glass contains traces of arsenic, but analyses, which are carefully checked by blank analyses, will obviate this difficulty. Only the best glass should be selected for this work. A portion of the glass is surrounded by nichrome wire gauze, which not only gives a more even distribution of heat but also helps support the glass tube and makes it very durable. On either side and above the gauze there is placed a piece of asbestos, which keeps a given area of the tube cherry red when a Meker burner is used as the source of heat. The entire tube is supported on a tripod. The part of the tube extending beyond the flame is cooled by using absorbent cotton, which is wound around the tube and attached to the end of a dropping funnel containing ice water. The water is allowed to drip slowly and thus cool the tube at the place of deposition of arsenic. It also gives a more uniform area of deposition of arsenic.

Twenty grams of mossy, or stick, zinc are placed in the bottle and dilute sulphuric acid is allowed to enter the bottle. A moderate evolution of hydrogen should be obtained. A too violent evolution should be avoided for two reasons: First, the formation of hydrogen sulphide, and, secondly, the formation according to some authorities of zinc sulphide which is deposited at the place where the mirror is observed. This grayish-white deposit may appear in some of the blank experiments and may lead to confusion in making comparisons. However, this may be avoided. The evolution of gas is allowed to continue until all the air is displaced from the apparatus. The tube is then heated to redness, and in testing reagents an evolution of gas lasting three or four hours may be allowed. Blanks are run in the same manner as the actual experiments, the evolution of gas lasting about an hour. The sample to be tested is allowed to run in very slowly, usually one drop in about three to five seconds. In most cases aliquot portions are used and these are diluted to 100

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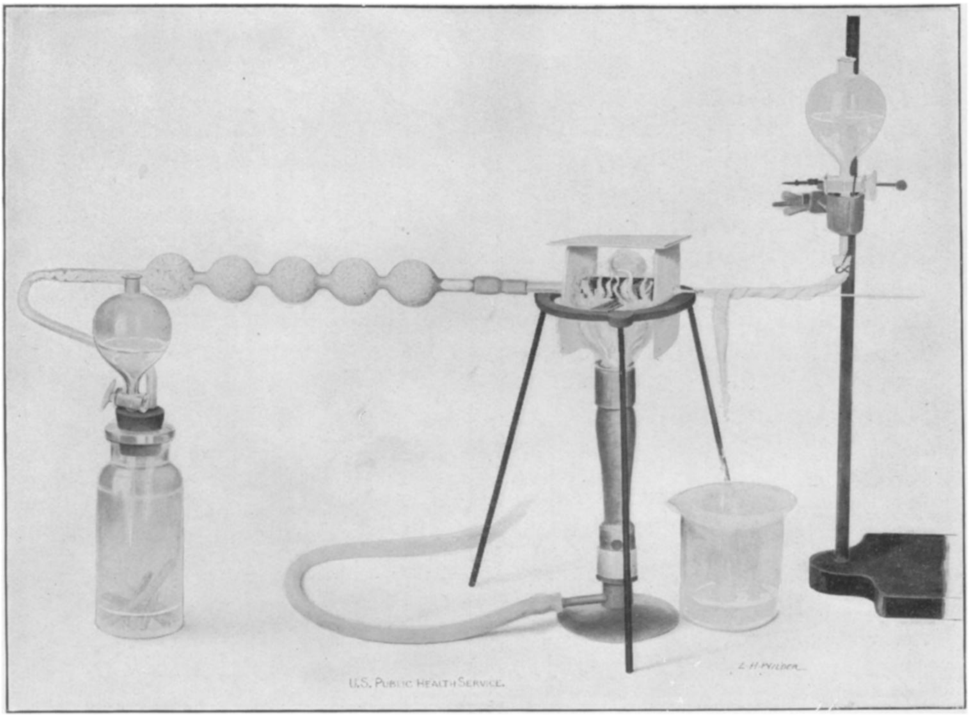

cubic centimeters. In this manner mirrors are obtained representing aliquot portions of the material to be tested, and these in turn are compared with the standard mirrors. The amount may then be expressed in milligrams or parts per million.

For the benefit of bacteriologists and medical men it has been suggested that an explanation be made to show the relation of weights and parts per million. A tenth normal solution of arsenic trioxide contains $4\frac{95}{100}$ grams of arsenic trioxide, but since the solution may be a trifle weak, or strong, the volumetric correction factor must be applied. By making the necessary dilutions a solution is obtained which contains 0.000001 gram of metallic arsenic in each cubic centimeter. Now use 1, 2, 3, 4, etc., cubic centimeters of this solution and the mirrors obtained in this manner will contain 0.000001, 0.000002, etc. grams of metallic arsenic. Taking into consideration the aliquot portion and the weight of the sample, the result will then be expressed in parts per million of metallic arsenic, or the results may be expressed in per cent, since the results are first obtained in terms of grams of arsenic. One precaution should be emphasized and that is to avoid the error of dilution, which is multiplicative, and in every case to use large quantities which will materially reduce this error. By moving the decimal point one place to the left in the tables the results will be expressed in parts per million.

The gaseous compounds which may be formed in the generator are $H_2S$, $H_2Se$, $H_2Te$, $H_3P$, $H_3Sb$, $H_3As$. These are all disposed of during the destruction of the organic matter, with the exception of $H_2S$, which is removed as described above. The garlic-like odor is readily detected by the sense of smell, and amounts as small as 1 or 2 parts in 10,000,000 can be detected. This odor will assist quite readily in determining the rate of evolution. It is possible to lose considerable arsenic in this manner unless the evolution of hydrogen gas is carefully controlled. The accompanying plate shows the manner in which the material is treated by the Marsh method.

The following tables show the amounts of arsenic which were found in blood clot, blood serum, and spinal fluid obtained after the administration of arsenobenzol, salvarsan, and neosalvarsan to patients having tabes dorsalis. The clinical side of these cases is not discussed in connection with this paper, which presents only the chemical findings observed at different intervals after administration. The clinical work was carried on by Dr. J. H. Barbat, whose discussion can be found in the references given in the bibliography.

**In years to come Liberty Loan securities will be harder to get and higher in price.**

| Date. | Patient. | Drug. | Amount of drug in gm. | Specimen. | Time obtained after administration of drug. | Arsenic content in mg. per 100 gms. of specimen. |
|---|---|---|---|---|---|---|
| Nov. 18, 1916 | Mrs. A. C., carcinoma. | Salvarsan | 0.5 | Blood A. Serum<br>B. Clot | 24 hours<br>24 hours | A. 0.200<br>B. 0.020 |
| Nov. 24, 1915 | Lett. Gen. Hosp. | Neosalvarsan | 0.9 | Blood A. Serum<br>B. Clot | 1 hour<br>1 hour | A. 0.400<br>B. 0.320 |
| Nov. 24, 1915 | Lett. Gen. Hosp. | Salvarsan | 0.6 | Blood A. Serum<br>B. Clot | 1 hour<br>1 hour | A. 1.700<br>B. 0.100 |
| Dec. 1, 1915 | Lett. Gen. Hosp. | Salvarsan | 0.6 | Blood A. Serum<br>B. Clot | 1 hour<br>1 hour | A. 0.500<br>B. 0.200 |
| Jan. 15, 1916 | C. D. S., tabes | Neosalvarsan | 0.9 | Spinal fluid | 48 hours | 0.025 |
| Mar. 8, 1916 | R. H., tabes | Arsenobenzol | 0.4 | Blood Serum<br>Clot<br>Spinal fluid. First<br>Second | 1 hour<br>30 minutes<br>24 hours | A. 0.700<br>B. 0.050<br>D. Trace.<br>C. 0.277 |
| Mar. 24, 1916 | R. H | Arsenobenzol | 0.4 | Spinal fluid. A<br>B | Immediately<br>24 hours | A. Trace.<br>B. 0.021 |
| Mar. 8, 1916 | S. O., tabes | Arsenobenzol | 0.4 | Blood A. Serum<br>B. Clot<br>Spinal fluid. C. First<br>D. Second | 1 hour<br>30 minutes<br>24 hours | A. 0.900<br>B. 0.100<br>C. 0.013<br>D. 0.038 |
| Mar. 24, 1916 | S. O | Arsenobenzol | 0.4 | Spinal fluid. A<br>B | Taken immediately.<br>24 hours | A. 0.021<br>B. 0.029 |
| Apr. 4, 1916 | G. S | Arsenobenzol | 0.4 | Spinal fluid. A<br>B | ½ hour<br>24 hours | A. 0.008<br>B. 0.008 |
| Mar. 8, 1916 | G. S | Arsenobenzol | 0.4 | Blood A. Serum<br>B. Clot<br>Spinal fluid. C. First<br>D. Second | 1 hour<br>30 minutes<br>24 hours | A. 1.000<br>B. 0.300<br>C. Trace.<br>D. 0.048 |
| Apr. 18, 1916 | G. S | Arsenobenzol | 0.4 | Spinal fluid. A<br>B | ½ hour<br>24 hours | A. 0.009<br>B. 0.010 |
| May 3, 1916 | G. S | Arsenobenzol | ........ | Spinal fluid | ½ hour | Trace. |
| Mar. 14, 1916 | Mc | Arsenobenzol | 0.4 | Blood A. Serum<br>B. Clot<br>Spinal fluid. C. First<br>D. Second | ............<br>............<br>............<br>............ | A. 0.400<br>B. 0.300<br>C. 0.028<br>D. 0.025 |
| Mar. 29, 1916 | Mc | Arsenobenzol | 0.4 | Spinal A<br>B | ½ hour<br>24 hours | A. Trace.<br>B. 0.010 |
| Mar. 15, 1916 | C. L. C | Arsenobenzol | 0.4 | Blood A<br>B<br>Spinal fluid C<br>D | 1 hour<br>1 hour<br>30 minutes<br>24 hours | A. 0.600<br>B. 0.400<br>C. ....<br>D. 0.080 |
| Mar. 29, 1916 | C. L. C | Arsenobenzol | 0.4 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. 0.003<br>B. 0.010 |
| Apr. 12, 1916 | C. L. C | Arsenobenzol | 0.6 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. Trace.<br>B. 0.006 |
| Apr. 25, 1916 | C. L. C | Arsenobenzol | 0.6 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. Trace.<br>B. 0.018 |
| Mar. 24, 1916 | B. D | Arsenobenzol | 0.4 | Spinal fluid A<br>B | Immediately<br>24 hours | A. 0.020<br>B. 0.040 |
| Apr. 4, 1916 | B. D | Arsenobenzol | 0.4 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. ....<br>B. 0.008 |
| Apr. 18, 1916 | B. D | Arsenobenzol | 0.4 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. 0.004<br>B. 0.004 |
| May 3, 1916 | B. D | Arsenobenzol | 0.6 | Spinal fluid A<br>B | ½ hour<br>48 hours | A. Trace.<br>B. 0.011 |
| Apr. 4, 1916 | R. H | Arsenobenzol | 0.4 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. ....<br>B. .... |
| Apr. 18, 1916 | R. H | Arsenobenzol | 0.6 | Spinal fluid A<br>B | ½ hour<br>24 hours | A. ....<br>B. Trace. |
| May 3, 1916 | R. H | Arsenobenzol | 0.6 | Spinal fluid A<br>B | Immediately<br>48 hours | A. ....<br>B. 0.010 |
| Mar. 8, 1916 | P. C., tabes | Arsenobenzol | 0.4 | Blood A. Serum<br>B. Clot<br>Spinal fluid C. 1st<br>D. 2nd | 1 hour<br>1 hour<br>30 minutes<br>24 hours | A. 0.668<br>B. 0.290<br>D. 0.062<br>C. 0.236 |
| Mar. 24, 1916 | P. C | Arsenobenzol | 0.4 | Spinal fluid A<br>B | Immediately<br>24 hours | A. ....<br>B. 0.054 |
| Apr. 4, 1916 | P. C | Arsenobenzol | 0.4 | Spinal fluid A<br>B | ½ hour<br>24 hours | ..........<br>0.050 |
| Apr. 18, 1916 | P. C | Arsenobenzol | 0.6 | Spinal fluid A<br>B | ½ hour<br>24 hours | ..........<br>0.008 |
| May 3, 1916 | P. C | Arsenobenzol | 0.6 | Spinal fluid A<br>B | ½ hour<br>48 hours | 0.003<br>0.004 |

**The Fifth Liberty Loan—A Peace Loan, A Victory Loan, A Memorial Loan.**

*Summary.*—This method, essentially a modification of the Lockemann method, is applicable for the determination of small amounts of arsenic in organic material. It gives excellent results when applied to urine, blood, serum, etc.

The method gives best results when applied to samples or aliquots containing 1 to 7 parts per million.

All samples should be weighed, rather than measured, when analysis is to be carried out.

The amount of arsenic found in these fluids was largest in the serum and least in the spinal fluid.

Barbat (1918) draws the following conclusions: "Analyses showed that the blood serum contained more than five times as much arsenic as the clot contained and that it averaged only about 8 parts per million. This fact proved that within half an hour after the administration of 0.4 gram of salvarsan 75 per cent is fixed in the body cells. The second portion of spinal fluid, which was withdrawn immediately after the administration of the salvarsan, showed 31 per cent arsenic free and 27 per cent with a trace, while 42 per cent gave an average of 0.2 part per million. The spinal fluid withdrawn 24 hours later showed one case out of 26 arsenic free, two cases with a trace, and an average of 0.25 part per million in the remaining 23 cases. These figures would indicate that arsenic can be made to pass into the spinal fluid in more than 96 per cent of patients suffering from tabes or paresis by the technic which I have described."

Strictly speaking, the preceding tables show the absorption of arsenic after the administration of arsenobenzol and do not give a fair comparison with salvarsan. Chemically, salvarsan is a distinct type of a generic nucleus known as 3, 3′-Diamino-4, 4′-Dioxy-Arsenobenzene Dihydrochloride. The arsenobenzene used in these administrations has not been definitely identified. The physical properties are somewhat different from salvarsan. The arsenic content is also between 1 and 2 per cent lower.

[Note.—This work was carried out in the Division of Pharmacology and the author wishes to express appreciation to Prof. Carl Voegtlin for suggestions and cooperation.]

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## HOSPITALS AND DISPENSARIES FOR FREE TREATMENT OF VENEREAL DISEASES.

In response to repeated requests addressed to the Public Health Service for a list of hospitals and dispensaries where those infected with venereal disease may secure treatment free of charge, the following list of such places has been compiled:

Alabama:
Anniston—Venereal Disease Clinic, Smith Building.
Huntsville—Venereal Disease Clinic, Huntsville City Hospital.
Mobile—Venereal Disease Clinic, in city jail building.
Montgomery—Venereal Disease Clinic, Room 205, Bell Building.
Sheffield—Venereal Disease Clinic, Nitrate Plant No. 2.